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Original article

Usefulness of a healthcare database for epidemiological research in atrial fibrillation

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ABSTRACT

Background: Big data are gaining attention as a valuable resource for providing insights into a range of issues and questions in healthcare. We evaluated the capacity of a Japanese healthcare database to conduct epidemiological research in non-valvular atrial fibrillation (NVAF).
Methods and results: We examined data collected between April 2008 and September 2013 in a Japanese healthcare database. Prior to the risk factor analysis, we validated the criteria for defining the occurrence of a stroke, systemic embolic event (SEE), and intracranial bleeding event during the study period. The validity was considered appropriate based on the resulting high positive predictive values. The data of 18,998 NVAF patients demonstrated that the incidence rates of stroke, SEE, and any bleeding events were 2.2, 0.08, and 2.4 per 100 patient-years, respectively. In patients who had not been treated with an anticoagulant, incidence of stroke significantly increased in higher $CHADS_2$ or CHA_2DS_2-VASc score, 1.7 and 1.5 fold by 1 point increase, respectively. The use of a proton pump inhibitor (PPI) was also identified as an independent risk factor for stroke. In patients who had been treated with an anticoagulant, the independent risk factors for any bleeding events were hypertension, renal dysfunction, hepatic failure, medical history of stroke, older age (≥65 years), use of nonsteroidal anti-inflammatory drug, and PPIs.
Conclusion: The data obtained in this study were comparable with results obtained in prospective cohort studies conducted in Japan.

Introduction

Atrial fibrillation (AF) is a common type of tachyarrhythmia that both cardiovascular specialists and general clinicians frequently encounter in clinical practice. Associated with a wide variety of symptoms, AF reduces quality of life because of palpitations and chest discomfort, among other symptoms, and often causes deterioration of heart function and thromboembolism. Along with its increasing prevalence, in particular in the aging population, and being a risk factor for ischemic stroke and systemic embolic events (SEE), AF is a key arrhythmia requiring daily clinical management.

Management involving antithrombotic therapy, heart rate control, restoration of sinus rhythm, and prevention of AF recurrence is a standard treatment for AF patients [1,2], and it

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has been recommended by the recent treatment guidelines for AF from the Japanese Circulation Society [3]. The treatment of non-valvular atrial fibrillation (NVAF) requires antithrombotic therapy to reduce the incidence of stroke and SEE, but this treatment must be carefully managed to prevent bleeding events.

According to one report, 1.6% of thromboembolic events occurred in AF patients in Japan [4]. Further, the prevalence of AF was twofold higher in men than women (2.4% vs. 1.2%) in this community-based cohort study conducted in 2006 in residents of Kurashiki City aged 40 years or older and undergoing an annual medical examination.

Some 1.5 to 2 million Japanese people are estimated to have AF. Although insights into the prognosis of AF in Japan have come from the J-RHYTHM Registry [5–11] and the Fushimi AF Registry [1,12–16], which have published extensive analyses, gaps in knowledge remain. Although randomized, large-scale studies provide the best evidence for guiding treatment, the relatively small prevalence of AF in Japan and the relatively low incidence of thromboembolic events and bleeding events associated with AF and anticoagulation therapy makes such a study challenging and expensive.

Therefore, we conducted the present study to determine whether an established healthcare database could be used to investigate risk factors for stroke, SEE, and bleeding events in the setting of NVAF, rather than a large-scale study. Employing an approach previously described [17], we first validated the parameters to be used to define thromboembolic and bleeding events (validation study) and then used the validated definitions to identify risk factors for these events.

Methods

Medical data for inpatients and outpatients who presented with AF between April 1, 2008 and September 30, 2013 were extracted from the healthcare database called EBM Provider®, which was constructed and managed by Medical Data Vision Co., Ltd. (Tokyo, Japan). This healthcare database includes data from 100 acute-care medical institutions in Japan, all of which are members of the Diagnosis Procedure Combination (DPC) reimbursement system, corresponding to 8% of all Japanese acute-care medical institutions, without geographic bias. Accordingly, this healthcare database was considered to have a suitable representation of patients with AF, who usually present to an acute-care hospital for an event.

The outcome measures for the present study were stroke, SEE, and bleeding events, as defined by parameters that could be mined from the healthcare database (bleeding requiring transfusion, intracranial bleeding, intraocular bleeding, upper gastrointestinal bleeding, and lower gastrointestinal bleeding).

Data extracted were: anonymized patient identifier, sex, and age, and, using the International Classification of Disease, Tenth Revision (ICD-10) codes, diagnoses, comorbidities at admission, etc. In addition, using Japanese public health insurance coding, data were extracted for procedures, drugs, implants, and extracted volume of blood transfusion, length of stay, in-hospital mortality, hospital charges, hospital department, date of medical service, date of hospitalization, orders for medical procedures and tests, surgeries, prescriptions, and laboratory values (less than 20% of patients). The EBM Provider® has been used previously in several epidemiology studies [18,19]. In this study, patients with AF were defined as those who had an ICD-10 AF-related code in their medical record (I48, excluding atrial flutter and post-operative AF).

First, as recommended by the Guidelines for Epidemiological Studies for Safety Assessments of Medicines Using a Healthcare Database [20], prior to the present analysis, we conducted a validation study of our definition of each type of event and the positive predictive value (PPV) of the definition. For the definition of stroke and SEE, 50 stroke events and 30 SEEs were randomly extracted from the database for validation. The number of extracted cases for validation is based on feasibility, not on statistical reasons. The definition of bleeding events had been validated recently by three orthopedists and a specialist in venous thromboembolism [17]. Thus, in the present study only the definition for intracranial bleeding was validated, using 20 intracranial bleeding events randomly extracted from the database, because a relatively low PPV (44.4%) was obtained in our previous validation study.

Second, we conducted an analysis of the capacity of the validated definitions of events to identify risk factors of stroke, SEE, and bleeding events in patients with NVAF. To ensure a post-diagnostic observation period of at least 2 years, patients who had been diagnosed with NVAF as of April 1, 2011 were included in this analysis. We excluded patients who had an event in the 3 months prior to the first day of the observation period, because of the possibility that their diagnosis was made after events occurred. Consequently, to evaluate the incidence of thrombotic events, bleeding events, and baseline risk factors, this analysis included patients diagnosed with NVAF between April 1, 2008 and December 31, 2010, and who were followed for at least 180 days from the date when medical data were first collected to allow for assessment of exposure and confounding factors.

Exclusion criteria were termination of medical data collection at the hospital, or prosthetic valve replacement before March 31, 2011. The starting date of the observation period was defined as the date of the earliest recorded NVAF episode, and the ending date was the last day information was recorded in the medical record or the date of the patient's death.

Statistical analysis

Stroke, SEE, and bleeding events were defined using information that could be extracted from the healthcare database. An event was defined if it was possible to extract the data from the database, regardless of the presence or absence of clinical laboratory data (Table S1). The PPV was defined as a percentage of events judged as clinically confirmed by the physicians. Then the exact (Clopper–Pearson) 95% confidence interval was estimated. The target PPV was between 60% and 70%, according to the methodology described by Kokotailo and Hill [21] and Andrade and colleagues [22].

To analyze the demographics for the two patient groups with and without anticoagulant therapy during the 180-day period before the start of the observation period, frequency tables were created for categorical parameters, while summary statistics were calculated for continuous variables. The cumulative incidence and incidence rate were calculated for stroke, SEE, and bleeding events. The incidence rate for each event was expressed as the number of events per 100 person-years and analyzed using the Cox proportional hazards regression model involving risk factors of stroke, SEE, and bleeding events.

Multivariable models were constructed by the backward elimination method. A P-value <0.05 was used as the criterion for variable selection. Three multivariable models were used in risk factor analysis for stroke and SEE in the non-anticoagulant agent group. In model 1, individual risk factor components of the CHA_2DS_2-VASc [23] and $CHADS_2$ [24] scores as separate explanatory variables were used; additionally, cardiomyopathy, age ($\geq$65 years and $<$75 years), vascular diseases (prior myocardial infarction, aortic plaque, and peripheral arterial disease identified by the JCS guideline [3]), and statin use, proton pump inhibitor (PPI) use, antiplatelet agents use were included in the model. In model 2, the components of the CHA_2DS_2-VASc score and the additional factors described for model 1 were evaluated. In model 3, the components of the $CHADS_2$ score and the additional factors described for model 1 were evaluated.

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